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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,562	11/14/2001	Avi J. Ashkenazi	P2730P1C18	2836

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EXAMINER

SPECTOR, LORRAINE

ART UNIT	PAPER NUMBER
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1647

DATE MAILED: 05/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/990,562

**Applicant(s)**

ASHKENAZI ET AL.

**Examiner**

Lorraine Spector, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 12 November 2004.  
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.  
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 119-121 and 123 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.  
6) ☒ Claim(s) 119-121 and 123 is/are rejected.  
7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.  
8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.  
10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)  
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)  
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 11/12/2004.  
4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.  
5) ☐ Notice of Informal Patent Application (PTO-152)  
6) ☐ Other: \_\_\_\_\_.

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**Part III: Detailed Office Action**

Claims 119-121 and 123 are pending and under consideration. The claims are drawn to antibodies that bind PRO1111 protein.

The rejection of claims under 35 U.S.C. 112, second paragraph is withdrawn in view of applicants amendment.

**Formal Matters:**

The new title of the invention is acknowledged.

**IDS:**

The information disclosure statement, filed 11/12/2004, has been considered.

**Priority Determination:**

The utility for the claimed protein is active in a chondrocyte redifferentiation assay. Applicants have established that the PCT application contains the chondrocyte redifferentiation. Accordingly, priority is set at 3/30/00.

Applicants argument that priority is merited to 8/17/1998 has been fully considered but is not deemed persuasive. Applicants argue that the disclosure that PRO1111 has homology to LIG-1 provides utility. This argument has been fully considered but is not deemed persuasive because applicants have not disclosed *what* utility they feel is conferred by that identification.

Applicants have argued in the paper filed 11/8/2004 that priority is merited to at least June 23, 1999 on the basis of gene amplification. This argument has been fully considered but is not deemed persuasive for reasons cited below:

At page 6, applicants argue that both the Examiner and Sen teach that aneuploid tissues are cancerous or pre-cancerous. This argument has been fully considered but is not deemed persuasive. Applicants statement is erroneous. Sen includes no teaching that all aneuploid tissues are cancerous or pre-cancerous, nor did the Examiner make any such statement. Rather, both Sen and the Examiner state that cancerous tissues are known to be aneuploid. It is also true

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that pre-cancerous tissues *may* be aneuploid. The converse is *not* true. Aneuploidy is also a feature of damaged tissue, and is commonly found in colon and lung tissues, which are subject to environmental damage. It does not invariably lead to cancer. Further, it remains that the 2-3 fold amplification of the nucleic acid is not predictive of a similar differential in protein expression; hence, the argument is not persuasive, as the claims are drawn to polypeptides, not the nucleic acids that encode them.

The Ashkenazi declaration filed under 37 CFR § 1.132 (and referred to at pages 10-11) argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would be useful. However, there is no evidence as to whether the gene *products* (such as the claimed polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial. Contrary to the statement referred to by applicants, there has been not “significant difference relative to normal tissue” established for PRO1111 protein, nor is such predictable from a 2-3fold amplification of the nucleic acid encoding such in a minority of tested samples.

Applicants argument of the Pennica reference at page 6 of the response has been fully considered but is not deemed persuasive. Applicants have plucked a single phrase from the portion cited by the Examiner, which phrase supports their assertion of utility. However, they have taken that phrase out of context; the teachings of Pennica as a whole support the opposite conclusion, that utility of the polypeptide cannot be predicted based upon amplification of the nucleic acid, for reasons set forth at pages 3-4 of the previous office action.

Applicant argues at page 7 that the Examiner has improperly generalized the teachings of Pennica and Konopka. This argument has been fully considered but is not deemed persuasive because both references are cited to establish the state of the art, which is that it is not predictable that a protein will be significantly amplified based upon a minor amplification of the nucleic acid encoding it. It is necessary to cite specific examples to form a general argument.

At pages 7-8, applicants argue that the Haynes reference establishes a general trend, and that few data points deviated from the expected, and thus that Haynes shows that the data meet a

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“more likely than not” standard of predictability. This argument has been fully considered but is not deemed persuasive because Figure 1 of Haynes, argued by applicants, shows data correlating *protein and mRNA* levels, not genomic DNA levels and protein. Applicants have not provided any mRNA data for PRO1111. Only DNA levels are provided, no mRNA or protein levels. Accordingly, the data in the specification as filed cannot be correlated with those of Haynes. Further, the figure clearly has a tight cluster of data points showing little or not protein expression at the region corresponding to 2-3 copies of mRNA. However, the principle for which Haynes was originally cited by the Examiner still applies: Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). That is Haynes’ conclusion, not the Examiner’s. The ‘general trend’ pointed to by applicants is seen at a level of mRNA copy number that has not been established for PRO1111, nor is it predictable from the observation of 2-3 copies of *DNA* per cell.

Applicants argument at page 8 that there is expected to be a correlation between gene amplification and protein overexpression, with reference to an article by Orntoft et al., has been fully considered but is not deemed persuasive. Orntoft et al. *could only compare the levels of about 40 well-resolved and focused abundant proteins.*” (See abstract.) It would appear that applicants have provided no fact or evidence concerning a correlation between such low levels of amplification of DNA, found only in a minority of tested tumors which were not characterized on the basis of those in the Orntoft publication, and an associated rise in level of the encoded protein. The Hyman reference cited by applicants found 44% of *highly* amplified genes showing overexpression at the mRNA level, and 10.5% of highly overexpressed genes being amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of SEQ ID NO: 228 would be correlated with elevated levels of mRNA. Further, Hyman does not examine protein expression. Applicants are reminded that the instant claims are directed to proteins. Similarly, Pollack, cited by applicants, does not analyze protein levels, nor does Pollack support the assertion that it is predictable, on the basis of the

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minimal increase in copy number of SEQ ID NO: 228 that the protein would accordingly be found at altered levels. Accordingly, it remains that the significance of the gene amplification data is questionable, and cannot be predictably extrapolated as applying to the claimed protein. The art, taken as a whole, clearly teaches that it is not predictable that a two-fold copy increase in the nucleic acid would translate to detectable over-expression of the associated mRNA, much less any protein encoded thereby. Further, as evidenced by the Orntoft publication, the type of data presented in the instant specification clearly does not meet the standard in the art for establishing association of a protein with cancer.

At page 9, Applicant presents a discussion of the declaration by Dr. Polakis filed under 37 CFR 1.132 with the response. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO1800 in tumor samples relevant to normal samples. Only gene amplification data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims 22-29, 35 and 37-41 based upon 35 U.S.C. §101 and §112, first paragraph, since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels, and not gene amplification levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature

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cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

As stated above, the Ashkenazi declaration filed under 37 CFR § 1.132 argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would be useful. However, there is no evidence as to whether the gene *products* (such as the claimed polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial.

Applicants argue (page 11) that Hanna et al. teaches that the HER-2/neu gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Applicant argues that the disclosed assay leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna et al. supports the instant rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Applicants arguments to the contrary fail to meet the urged “more likely than not” standard, but

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rather fall well within the category that significant further experimentation would be required to determine if the claimed polypeptides have the urged utility, experimentation of the type that was found to be impermissible by the court in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct. 1966).

**Rejections Over Prior Art:**

Priority is set at 3/30/00.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 119-121 remain rejected under 35 U.S.C. 102(a) as being anticipated by Jacobs, WO 99/50405. SEQ ID NO: 2 of the publication is 99.7% identical to SEQ ID NO: 229 of the instant application. Antibodies are disclosed beginning at page 77, and include monoclonal, polyclonal, humanized, chimeric, and single chain antibodies. At page 78 the disclosure states that the antibodies may be used for detection of protein. Accordingly, the claims are anticipated by Jacobs. Applicants argument pertaining to the priority date in the paper filed 11/12/2004 is not persuasive for reasons cited above with respect to priority date determination.

Claims 119-121 and 123 remain rejected under 35 U.S.C. 102(e) as being anticipated by Shimkets, U.S. Patent Number 6,689,866 or US Patent Application Publication US2003/0054514 A1, or US Patent Application Publication US2003/0003532 A1. The US Patent Application Publications are divisionals of the patent, and differ only in the claims. The '514 publication contains claims to nucleic acids, proteins (see claim 11), and antibodies (see claim 13), and the



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'532 application contains claims to nucleic acids and vectors. The teachings will be discussed with reference to the issued patent. SEQ ID NO: 9 of the patent is 99.7% identical to SEQ ID NO: 228 of the instant application, at bases 1-2183 (bases 159-2341 of the patent), and encodes a protein 99.2% identical to that of SEQ ID NO: 229. SEQ ID NO: 31 is a fragment of SEQ ID NO: 9, is identified as encoding the extracellular domain (see figures 17A and 17B), which is 100% identical to residues 45-495 of SEQ ID NO: 229. Antibodies are disclosed at column 36, and include monoclonal, polyclonal, humanized, chimeric, and single chain antibodies. Labeled antibodies are disclosed at column 37, lines 44-45. Accordingly, the claims are anticipated by Shimkets. Applicants argument pertaining to the priority date in the paper filed 11/12/2004 is not persuasive for reasons cited above with respect to priority date determination.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 119-120 and 123 remain rejected under 35 U.S.C. 103(a) as being obvious over any one of Loci AI769814, AI435407, AI470931, or T15752, in view of Sibson et al. for reasons cited in the previous Office Action mailed 7/1/2004, at page 7. Applicants argument pertaining to the priority date in the paper filed 11/12/2004 is not persuasive for reasons cited above with respect to priority date determination.

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Claim 121 remains rejected under 35 U.S.C. 103(a) as being obvious over any one of Loci AI769814, AI435407, AI470931, or T15752, in view of Sibson et al. and further in view of U.S. Patent Number 5,565,332 (Hoogenboom et al.) in the case of claim 121, or in view of U.S. Patent Number 4,946,778 (Ladner et al.) in the case of claim 122 for reasons cited in the previous Office Action mailed 7/1/2004, at pages 7-8. Applicants argument pertaining to the priority date in the paper filed 11/12/2004 is not persuasive for reasons cited above with respect to priority date determination.

Claim 123 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Jacobs, WO 99/50405 for reasons cited in the previous Office Action mailed 7/1/2004, at page 8. Applicants argument pertaining to the priority date in the paper filed 11/12/2004 is not persuasive for reasons cited above with respect to priority date determination.

**Advisory Information:**

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

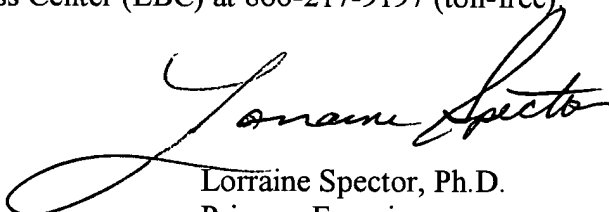
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to **571-273-0893**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Lorraine Spector, Ph.D.  
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